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Hierarchical modeling of Alzheimer's disease progression from a large longitudinal MRI data set

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Introduction

Untangling pathological processes from the natural inter-individual variability is a major challenge in Alzheimer's disease (AD): natural anatomical variability is often much larger than individual pathological alterations, hindering the identification of relevant disease markers. In a longitudinal MRI data set of subjects progressing from mild cognitive impairment (MCI) to AD, variability not only comes from baseline differences, but also from the individual dynamics of progression. Based on recent computational morphometry tools, [1] proposes to learn a hierarchical model from longitudinal shape data sets, where individual progressions are represented in terms of orthogonal spatial and temporal warps of a common reference progression. In this work, we extend this approach to 3D images to model the spatiotemporal progression of atrophy in AD starting from the prodromal stage. A long-term average scenario of progression to AD is learned, along with interpretable individual parameters of variability that we correlate with genetic and environmental co-factors.

Methods

We selected from the ADNI database all subjects meeting the following requirements: (i) diagnosed as MCI at a visit, (ii) diagnosed as AD at a later visit, (iii) never reverted from AD to MCI or from MCI to cognitively normal (CN). A total of 322 subjects fulfilled those criteria, representing 1993 visits with T1-weighted MRI (average number of visits: 5.8 (±2.4); age: 74.0 (±6.7) years; education level: 15.9 (±2.8) years; 41.2% females; 65.2% APOE-ε4 carriers; 80.9% married). Images were first processed with the longitudinal FreeSurfer pipeline [5] through the Clinica platform [6]. The resulting skull-removed intensity-normalized images were then affinely aligned onto the Colin27 reference brain [4] with the FSL software [7]. To reduce the computational burden, images were finally subsampled to a size of 64^3 voxels. The result was given as input to the longitudinal atlas pipeline of the Deformetrica software [2, 3] that implements the approach introduced in [1]. Outputs are composed of an average long-term scenario, along with low-dimensional parameters encoding how each individual differ from this normative scenario. The variability in the dynamics is represented for each individual by: (i) an estimated onset age that encodes the variability in the onset of the alterations, (ii) an estimated acceleration factor that encodes the variability in the pace of progression of those alterations.

Results

Figure 1 displays the estimated long-term scenario of progression to AD. The ventricles clearly increase in size and atrophy is visible in the insula and parietal sulci regions. Figure 2 plots the estimated individual onset ages against the actual ages at which AD diagnosis was made. The high correlation suggests that the model successfully captured the relative stages of development of the disease across patients. We studied the association between estimated onset ages and co-factors (gender, APOE-ε4 carriership, marital status and education level) through multivariate linear regression. Analysis of the estimated coefficients revealed that female subjects develop AD significantly earlier (by 31.2 (±18.4) months, p=0.0019), similarly to APOE-ε4 carriers vs. non-carriers (by 19.8 (±17.5) months, p=0.036) and married subjects vs. non-married (by 45.9 (±22.8) months, p=0.00038). The same analysis was performed for the estimated individual acceleration factors: we found that APOE-ε4 carriers progress significantly faster than non-carriers (by a factor of 1.14 (±0.09), p=0.010). Confidence intervals are at 95%, and p-values are FDR-corrected.

Conclusions

The learned hierarchical model provides both a normative long-term scenario of AD progression at the population level, and interpretable parameters encoding its dynamical variability at the individual level. This scenario is in line with current medical knowledge, and significant co-factors of progression can be identified from the individual parameters.

Acknowledgments

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Figures

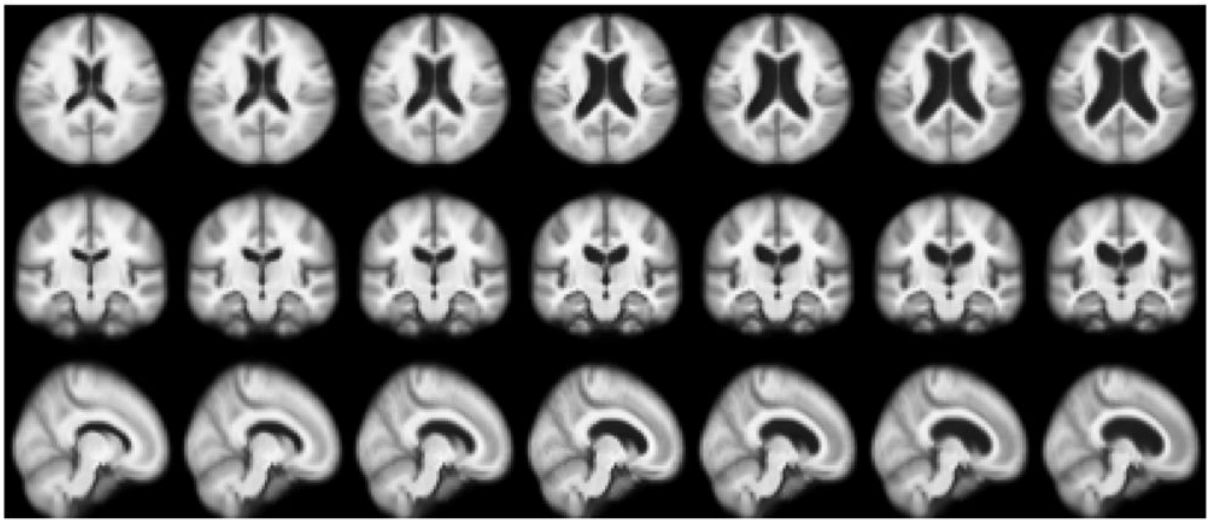

Figure 1. Estimated average scenario of progression to Alzheimer's disease. Left to right: ages 63, 67, 71, 75, 79, 83, and 87. Top to bottom: axial, coronal and saggital views.

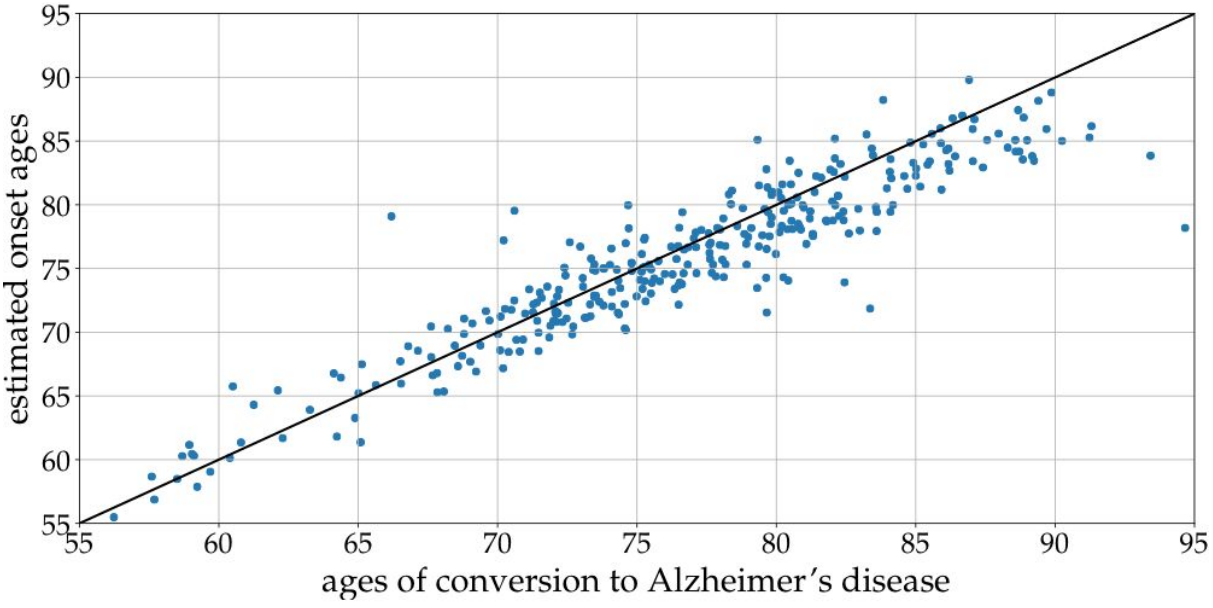

Figure 2. Estimated individual onset ages vs. the ages of conversion to Alzheimer's disease, for the considered 322 subjects (blue dots). The R^2 score is 0.80. The solid black line is the bisector.